Claims

1. A composition comprising

a conjugate of hyaluronic acid and a linking molecule that is a substrate of transglutaminase, and

free hyaluronic acid,

wherein the free hyaluronic acid and the conjugate are present in a molar ratio of at least 2.

2. The composition of claim 1, wherein the linking molecule has at least two contiguous aliphatic amines, at least three contiguous aliphatic amines, at least four contiguous aliphatic amines, at least five aliphatic amines, or at least six aliphatic amines.

3. The composition of claim 1, wherein the linking molecule is native polylysine.

4. The composition of claim 3, wherein polylysine is selected from the group consisting of poly-L-lysine, poly-D-lysine, and poly-DL-lysine.

5. The composition of claim 1, wherein the linking molecule is a derivative of polylysine.

6. The composition of claim 1, wherein the linking molecule has at least two continuous carboxamides, at least three contiguous carboxamides, at least four contiguous carboxamides, at least five carboxamides, or at least six carboxamides.

7. The composition of claim 1, wherein the linking molecule is native polyglutamine.

8. The composition of claim 7, wherein linking molecule is selected from the group consisting of poly-L-glutamine, poly-D-glutamine, and poly-DL-glutamine.

9. The composition of claim 1, wherein the linking molecule is a derivative of polyglutamine.

10. The composition of claim 1, wherein the hyaluronic acid is native hyaluronic acid.

11. The composition of claim 1, wherein the hyaluronic acid is a derivative of hyaluronic acid selected from the group consisting of a pharmaceutically acceptable salt of hyaluronic acid, a hyaluronic acid ester, and a sulfated hyaluronic acid.

12. The composition of claim 1, wherein the molar ratio is selected from the group consisting of at least 2.0 and at least 4.0.

13. The composition of claim 1, wherein the composition is provided in a form selected from the group consisting of an eye dropper, a contact lens solution, an ophthalmic ointment, an eye pack, and a contact lens.

14. The composition of claim 1, wherein the composition is provided in a form selected from the group consisting of a sublingual tablet, a mouthwash, a toothpaste, a candy, and an oral gel.

15. The composition of claim 1, wherein the hyaluronic acid has a molecular weight of at least 100,000.

16. The composition of claim 1, wherein the conjugate has a negative charge to positive charge ratio of greater than 1.0.

17. The composition of claim 1, further comprising a pharmaceutically acceptable carrier.

18. The composition of claim 17, wherein the pharmaceutically acceptable carrier comprises an ophthalmic preservative.

19. The composition of claim 18, wherein the ophthalmic preservative is selected from the group consisting of organic mercurials, quaternary ammonium compounds, parahydroxybenzoic acid esters, substituted alcohols and phenols.

20. The composition of claim 19, wherein the organic mercurial is selected from the group consisting of phenylmercuric nitrate, phenylmercuric acetate, phenylmercuric borate, and thimerosal.

21. The composition of claim 19, wherein the quaternary ammonium compound is selected from the group consisting of benzalkonium chloride, benzethonium chloride, cetyl pyridinium chloride, and polyquaternium-1 (POLYQUAD).

22. The composition of claim 19, wherein the substituted alcohol and phenol is selected from the group consisting of chlorobutanol, and chlorobutanol/phenylethyl alcohol.

23. The composition of claim 18, wherein the ophthalmic preservative is an antibiotic.

24. The composition of claim 1, further comprising an agent selected from the group consisting of a flavoring agent, a coloring agent and a scenting agent.

25. The composition of claim 1, wherein the conjugate has a weight ratio selected from the group consisting of at least 90%, at least 95%, and at least 99%.

26. The composition of claim 1, further comprising arginine or fluoride.

27. The composition of claim 1, wherein the linking molecule is uncomplexed.

28. A pharmaceutical composition comprising

hyaluronic acid covalently linked to a linking molecule that is a substrate of transglutaminase,

wherein the linking molecule is uncomplexed.

29. The pharmaceutical composition of claim 28, wherein the linking molecule has at least two contiguous aliphatic amines, at least three contiguous aliphatic amines, at least four contiguous aliphatic amines, at least five aliphatic amines, or at least six aliphatic amines.

30. The pharmaceutical composition of claim 28, wherein the linking molecule is native polylysine.

31. The pharmaceutical composition of claim 30, wherein polylysine is selected from the group consisting of poly-L-lysine, poly-D-lysine, and poly-DL-lysine.

32. The pharmaceutical composition of claim 28, wherein the linking molecule is a derivative of polylysine.

33. The pharmaceutical composition of claim 28, wherein the linking molecule has at least two contiguous carboxamides, at least three contiguous carboxamides, at least four contiguous carboxamides, at least five carboxamides, or at least six carboxamides.

34. The pharmaceutical composition of claim 28, wherein the linking molecule is native polyglutamine.

35. The pharmaceutical composition of claim 34, wherein polylysine is selected from the group consisting of poly-L-glutamine, poly-D-glutamine, and poly-DL-glutamine.

36. The pharmaceutical composition of claim 28, wherein the linking molecule is a derivative of polyglutamine.

37. The pharmaceutical composition of claim 28, wherein the hyaluronic acid is native hyaluronic acid.

38. The pharmaceutical composition of claim 28, wherein the hyaluronic acid is a hyaluronic acid derivative selected from the group consisting of a pharmaceutically acceptable salt of hyaluronic acid, a hyaluronic acid ester, and sulfated hyaluronic acid.

39. The pharmaceutical composition of claim 28, further comprising free hyaluronic acid.

40. The pharmaceutical composition of claim 28, wherein the composition is provided in a form selected from the group consisting of an eye dropper, a contact lens solution, an ophthalmic ointment, an eye pack, and a contact lens.

41. The pharmaceutical composition of claim 28, wherein the composition is provided in a form selected from the group consisting of a sublingual tablet, a mouthwash, a toothpaste, a candy, and an oral gel.

42. The pharmaceutical composition of claim 28, wherein the hyaluronic acid has a molecular weight of at least 100,000.

43. The pharmaceutical composition of claim 28, wherein the conjugate has a negative to positive charge ratio of greater than 1.

44. The pharmaceutical composition of claim 28, further comprising a pharmaceutically acceptable carrier.

45. The pharmaceutical composition of claim 44, wherein the pharmaceutically acceptable carrier comprises an ophthalmic preservative.

46. The pharmaceutical composition of claim 45, wherein the ophthalmic preservative is selected from the group consisting of organic mercurials, quaternary ammonium compounds, parahydroxybenzoic acid esters, substituted alcohols and phenols.

47. The pharmaceutical composition of claim 46, wherein the organic mercurial is selected from the group consisting of phenylmercuric nitrate, phenylmercuric acetate, phenylmercuric borate, and thimerosal.

48. The pharmaceutical composition of claim 46, wherein the quaternary ammonium compound is selected from the group consisting of benzalkonium chloride, benzethonium chloride, cetyl pyridinium chloride, and polyquaternium-1 (POLYQUAD).

49. The pharmaceutical composition of claim 46, wherein the substituted alcohol and phenol is selected from the group consisting of chlorobutanol, and chlorobutanol/phenylethyl alcohol.

50. The pharmaceutical composition of claim 45, wherein the ophthalmic preservative is an antibiotic.

51. The pharmaceutical composition of claim 44 , wherein the pharmaceutically acceptable carrier has an osmolality of at least 280 mOsm.

52. The pharmaceutical composition of claim 44, wherein the pharmaceutically acceptable carrier has a pH of at least 6.5.

53. The pharmaceutical composition of claim 44, wherein the pharmaceutically acceptable carrier comprises arginine or fluoride.

54. The pharmaceutical composition of claim 28, wherein the conjugate has a weight ratio selected from the group consisting of at least 90%, at least 95%, and at least 99%.

55. A composition comprising

a conjugate of hyaluronic acid and a to a linking molecule that is a substrate of transglutaminase,

in an eye dropper bottle.

56. The composition of claim 55, further comprising a pharmaceutically acceptable carrier.

57. The composition of claim 55, further comprising instructions for use.

58. The composition of claim 55, wherein the linking molecule has at least two contiguous aliphatic amines, at least three contiguous aliphatic amines, at least four contiguous aliphatic amines, at least five aliphatic amines, or at least six aliphatic amines.

59. The composition of claim 55, wherein the linking molecule is native polylysine, or a derivative of polylysine.

60. The composition of claim 59, wherein native polylysine is selected from the group consisting of poly-L-lysine, poly-D-lysine, and poly-DL-lysine.

61. The composition of claim 55, wherein the linking molecule has at least two contiguous carboxamides, at least three contiguous carboxamides, at least four contiguous carboxamides, at least five carboxamides, or at least six carboxamides.

62. The composition of claim 55, wherein the linking molecule is native polyglutamine, or a derivative of polyglutamine.

63. The composition of claim 62, wherein native polyglutamine is selected from the group consisting of poly-L-glutamine, poly-D-glutamine, and poly-DL-glutamine.

64. The composition of claim 55, wherein the hyaluronic acid is native hyaluronic acid.

65. The composition of claim 55, wherein the hyaluronic acid is a hyaluronic acid derivative selected from the group consisting of a pharmaceutically acceptable salt of hyaluronic acid, a hyaluronic acid ester, and a sulfated hyaluronic acid.

66. The composition of claim 55, further comprising free hyaluronic acid.

67. The composition of claim 55, wherein the hyaluronic acid has a molecular weight of at least 100,000.

68. The composition of claim 55, wherein the conjugate has a negative charge to positive charge ratio in greater than 1.

69. The composition of claim 56, wherein the pharmaceutically acceptable carrier comprises an ophthalmic preservative.

70. The composition of claim 69, wherein the ophthalmic preservative is selected from the group consisting of organic mercurials, quaternary ammonium compounds, parahydroxybenzoic acid esters, substituted alcohols and phenols.

71. The composition of claim 70, wherein the organic mercurial is selected from the group consisting of phenylmercuric nitrate, phenylmercuric acetate, phenylmercuric borate, and thimerosal.

72. The composition of claim 70, wherein the quaternary ammonium compound is selected from the group consisting of benzalkonium chloride, benzethonium chloride, cetyl pyridinium chloride, and polyquaternium-1 (POLYQUAD).

73. The composition of claim 70, wherein the substituted alcohol and phenol is selected from the group consisting of chlorobutanol, and chlorobutanol/phenylethyl alcohol.

74. The composition of claim 69, wherein the ophthalmic preservative is an antibiotic.

75. The composition of claim 56 , wherein the pharmaceutically acceptable carrier has an osmolality of at least 280 mOsm.

76. The composition of claim 56, wherein the pharmaceutically acceptable carrier has a pH of at least 6.5.

77. The composition of claim 56 , wherein the pharmaceutically acceptable carrier comprises arginine or lysozyme.

78. The composition of claim 55, wherein the conjugate has a weight ratio selected from the group consisting of at least 90%, at least 95%, and at least 99%.

79. The composition of claim 55, wherein the linking molecule is uncomplexed.

80. A composition comprising

a conjugate of hyaluronic acid and a linking molecule that is a substrate of transglutaminase, and

an agent selected from the group consisting of a flavoring agent, a coloring agent and a scenting agent.

81. The composition of claim 80, wherein the flavoring agent is selected from the group consisting of mannitol, sodium saccharin, magnasweet, peppermint extract, leaf power or oil; spearmint extract, leaf powder or oil; wintergreen oil; vanilla extract; parsley; oregano oil; bay leaf oil; clove oil; sage oil; sassafras oil; lemon oil; orange oil; anise oil; benzaldehyde; almond oil; camphor; cedar leaf oil; marjoram oil; cintronella oil; lavender oil; mustard oil; pine oil; pine needle oil; rosemary oil; thyme oil; cinnamon leaf oil; menthol; carvone; anethole; eugenol; methyl salicylate; limonene; cymene; n-decyl alcohol; citronellol; α-terpineol; methyl acetate; citronellyl acetate; methyl eugenol; cineole; linalool; eyktl linalool; vanillin; thymol; pellira oil; gaultheria oil; eucalyptus oil; caffeine, cream of tartar, lactic acid, malic acid, monosodium glutamate, nitrites, sorbitol, aspartame, acesulfame, dextrose, levulose, sodium cyclamate, stevioside, neo-hesperidyl dihydrochalcone, glycyrrhizin, perillartine, thaumatin, aspartylphenylalanine methyl ester, and p-methoxycinnamic aldehyde.

82. The composition of claim 80, wherein the coloring agent is selected from the group consisting of FD&C Blue #1, FD&C Yellow #5, FD&C Yellow #10, FD&C Red #3, FD&C Red #40; caramel color or powder (#05439), chocolate shade (#05349), green lake blend (#09236), kowet titanium dioxide (#03970), yellow liquid color (#00403), and nitrites.

83. The composition of claim 80, wherein the scenting agent is selected from the group consisting of flower extract, herb extract, blossom extract, plant extract, and artificial scenting agents.

84. The composition of claim 80, wherein the composition is formulated for oral administration.

85. The composition of claim 84, wherein the composition is formulated as a sublingual tablet, a mouth wash, a toothpaste, an oral gel, and a candy.

86. The composition of claim 80, further comprising arginine or fluoride.

87. The composition of claim 80, further comprising a pharmaceutically acceptable carrier.

88. The composition of claim 87, wherein the pharmaceutically acceptable carrier has a pH of at least 6.5.

89. The composition of claim 80, wherein the linking molecule is uncomplexed.

90. The composition of claim 80, wherein the conjugate has a weight ratio selected from the group consisting of at least 90%, at least 95%, and at least 99%.

91. The composition of claim 87, wherein the pharmaceutically acceptable carrier has an osmolality of greater than 280 mOsm.

92. A composition comprising

a conjugate of hyaluronic acid and a linking molecule that is a substrate of transglutaminase,

in a carrier that comprises fluoride.

93. The composition of claim 92, further comprising a pharmaceutically acceptable carrier.

94. The composition of claim 93, wherein the pharmaceutically acceptable carrier has a pH of at least 6.5.

95. The composition of claim 92, wherein the linking molecule is uncomplexed.

96. The composition of claim 92, wherein the conjugate has a weight ratio selected from the group consisting of at least 90%, at least 95%, and at least 99%.

97. The composition of claim 93, wherein the pharmaceutically acceptable carrier has an osmolality of greater than 280 mOsm.

98. The composition of claim 92, wherein the conjugate is provided in a form selected from the group consisting of a sublingual tablet, a mouthwash, a toothpaste, a candy, and an oral gel.

99. A composition comprising

a conjugate of hyaluronic acid and a to a linking molecule that is a substrate of transglutaminase,

in a sublingual tablet form.

100. The composition of claim 99, further comprising a sweetener selected from the group consisting of saccharin, aspartame, sorbitol, acesulfame, dextrose, levulose, sodium cyclamate, stevioside, neo-hesperidyl dihydrochalcone, glycyrrhizin, perillartine, thaumatin, aspartylphenylalanine methyl ester, and p-methoxycinnamic aldehyde.

101. The composition of claim 99, further comprising a vitamin.

102. The composition of claim 99, further comprising fluoride.

103. A method for treating an disorder characterized by dryness comprising administering an effective amount of the composition of claim 1, 28, 55, 80, 92 or 99 to a subject in need thereof.

104. The method of claim 103, wherein the disorder is dry eye.

105. The method of claim 103, wherein dry eye associated with a disorder selected from the group consisting of nonprogressive conjunctival cicatrization (Stevens-Johnson syndrome), Sjögren's syndrome, trachoma, and cicatricial pemphigoid.

106. The method of claim 103, wherein the disorder is dry mouth.

107. A pharmaceutical composition comprising

a conjugate of hyaluronic acid and a linking molecule that is a substrate of transglutaminase, and

an effective amount of free hyaluronic acid,

wherein the free hyaluronic acid and the conjugate are present in a molar ratio of at least 2.

108. A method for treating a subject comprising

administering to an eye of a subject having or at risk of having dryness of the eye an effective amount of a conjugate of hyaluronic acid and a linking molecule that is a substrate of transglutaminase.

109. The method of claim 108, wherein the conjugate is provided in a form selected from the group consisting of an eye dropper, a contact lens solution, an ophthalmic ointment, an eye pack, and a contact lens.

110. A method of treating a subject comprising

administering to an oral cavity of a subject having or at risk of having dryness of the oral cavity an effective amount of a conjugate of hyaluronic acid and a linking molecule that is a substrate of transglutaminase.

111. The method of claim 110, wherein the conjugate is provided in a form selected from the group consisting of a sublingual tablet, a mouthwash, a toothpaste, a candy, and an oral gel.

112. A method of treating a subject comprising

administering to a joint of a subject having or at risk of having joint discomfort an effective amount of a conjugate of hyaluronic acid and a linking molecule that is a substrate of transglutaminase.

113. A method of treating a subject comprising

administering to a blood vessel of a subject having or at risk of having excessive blood clotting or having an elevated risk of blood clotting an effective amount of a conjugate of hyaluronic acid and a linking molecule that is a substrate of transglutaminase.

114. A method of treating a subject comprising

administering to skin of a subject having or at risk of having wrinkles an effective amount of a conjugate of hyaluronic acid and a linking molecule that is a substrate of transglutaminase.

115. The method of claim 108, 110, 112, 113 or 114, wherein the effective amount is less than 0.05 μg/kg per day.

116. The method of claim 108, 110, 112, 113 or 114, wherein the linking molecule has at least two contiguous aliphatic amines, at least three contiguous aliphatic amines, at least four contiguous aliphatic amines, at least five aliphatic amines, or at least six aliphatic amines.

117. The method of claim 108, 110, 112, 113 or 114, wherein the linking molecule is native polylysine.

118. The method of claim, wherein polylysine is selected from the group consisting of poly-L-lysine, poly-D-lysine, and poly-DL-lysine.

119. The method of claim 108, 110, 112, 113 or 114, wherein the linking molecule is a derivative of polylysine.

120. The method of claim 108, 110, 112, 113 or 114, wherein the linking molecule has at least two continuous carboxamides, at least three contiguous carboxamides, at least four contiguous carboxamides, at least five carboxamides, or at least six carboxamides.

121. The method of claim 108, 110, 112, 113 or 114, wherein the linking molecule is native polyglutamine.

122. The method of claim 108, 110, 112, 113 or 114, wherein linking molecule is selected from the group consisting of poly-L-glutamine, poly-D- glutamine, and poly-DL-glutamine.

123. The method of claim 108, 110, 112, 113 or 114, wherein the linking molecule is a derivative of polyglutamine.

124. The method of claim 108, 110, 112, 113 or 114, wherein the hyaluronic acid is native hyaluronic acid.

125. The method of claim 108, 110, 112, 113 or 114, wherein the hyaluronic acid is a derivative of hyaluronic acid selected from the group consisting of a pharmaceutically acceptable salt of hyaluronic acid, a hyaluronic acid ester, and a sulfated hyaluronic acid.

126. The method of claim 108, 110, 112, 113 or 114, wherein the hyaluronic acid has a molecular weight of at least 100,000.

127. The method of claim 108, 110, 112, 113 or 114, wherein the conjugate has a negative charge to positive charge ratio of greater than 1.0.

128. The method of claim 108, 110, 112, 113 or 114, wherein the conjugate is administered in a pharmaceutically acceptable carrier.

129. The method of claim 108, wherein the conjugate is administered in a pharmaceutically acceptable carrier that comprises an ophthalmic preservative.

130. The method of claim 129, wherein the ophthalmic preservative is selected from the group consisting of organic mercurials, quaternary ammonium compounds, parahydroxybenzoic acid esters, substituted alcohols and phenols.

131. The method of claim 129, wherein the organic mercurial is selected from the group consisting of phenylmercuric nitrate, phenylmercuric acetate, phenylmercuric borate, and thimerosal.

132. The method of claim 129, wherein the quaternary ammonium compound is selected from the group consisting of benzalkonium chloride, benzethonium chloride, cetyl pyridinium chloride, and polyquaternium-1 (POLYQUAD).

133. The method of claim 129, wherein the substituted alcohol and phenol is selected from the group consisting of chlorobutanol, and chlorobutanol/phenylethyl alcohol.

134. The method of claim 128, wherein the ophthalmic preservative is an antibiotic.

135. The method of claim 110, wherein the conjugate is administered in a pharmaceutically acceptable carrier that comprises an agent selected from the group consisting of a flavoring agent, a coloring agent and a scenting agent.

136. The method of claim 108, 110, 112, 113 or 114, wherein the conjugate has a weight ratio selected from the group consisting of at least 90%, at least 95%, and at least 99%.

137. The method of claim 128, wherein the pharmaceutically acceptable carrier comprises arginine.

138. The method of claim 128, wherein the pharmaceutically acceptable carrier has a pH of at least 6.5.

139. The method of claim 128, wherein the pharmaceutically acceptable carrier has an osmolality of at least 280 mOsm.